32| Biomarkers of Accelerated Aging in Severe Mental Illness (Part 2) – With Dr. Lisa Eyler

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Lisa Eyler, John Bellone, Ryan Van Patten

Intro Music 00:00

John Bellone 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior. I'm John Bellone...

Ryan Van Patten 00:23

...and I'm Ryan Van Patten. Today we have Part 2 of our conversation with Lisa Eyler. So be sure that you have listened to Part 1, which is the previous episode that we released before listening to this part today. There's important prerequisites, concepts, and terms that we talked about last time that you'll need to have listened to first.

John Bellone 00:43

And we're also going to come on right after the conversation with her. We'll bring you some of our commentary - our thoughts about some of the things that came up and some other things that have been on our mind.

Ryan Van Patten 00:54

And, with that, we bring you Part 2 of our conversation with Lisa.

Transition Music 00:58

Ryan Van Patten 01:07

I want to move into neuroimaging as we had discussed, and bring that into the aging conversation. So I'll start by asking, you had mentioned resting state functional connectivity, so how might functional connectivity be altered as we age?

Lisa Eyler 01:26

There's a couple of different ways that it can be altered, but the most often observed is that there's less integrity of these functional connections, so to speak, so that the correspondence between the signals in two different regions is less tight. So the idea is that this may reflect structural connectivity. That there may actually be fewer neuronal connections between these regions, or perhaps a decrease in myelination of the axonal tracts between these regions. But it's shown in a decrease in the correlation between the BOLD signal in one region and another and that can be seen at rest and it can also be seen during tasks. So that's probably the most commonly observed thing in aging in terms of functional connectivity - it's this sort of decrease in the coherence of the signal across regions. This may be particularly seen in the set of regions that's often known as the default mode network. So the default mode network, for those that haven't heard of it, is basically a set of regions that are "on" when you're not doing something. Or another way of saying it is, it turns off when you are doing something with your brain, in

terms of either hearing a stimulus or thinking about something in particular. The regions also tend to co-activate or be coherent for a little bit more emotional, or autobiographical, or kind of rumination about things. And maybe the kind of things that you do when somebody tells you to just lay in the scanner for a while and do nothing. [laughs] You start thinking about what you had for dinner last night and what you're going to buy at the grocery store and... [laughs]

John Bellone 03:23
How loud the machine is that you're in. [laughs]

Ryan Van Patten 03:25
[laughs]

Lisa Eyler 03:25
Exactly. But in any case, this default mode network was actually discovered because a bunch of people started noticing that although different areas of the brain lit up depending on which kinds of tasks you were doing, there was a lot of areas that were turning off and they were all the same places - obviously, medial prefrontal cortex, posterior cingulate, angular gyrus on both sides, and then some people say hippocampus, although sometimes people include hippocampus in the DMN, the default mode network, and some people don't. So the default mode network was probably the place that has been looked at the most in terms of aging, and also comparing different disorders. And definitely there seems to be a reduction in coherence - for sure in Alzheimer's disease, a reduction of the correlation between those areas and their BOLD signal.

John Bellone 04:17
I'm curious about the literature on functional connectivity in SMI populations. So is there any data explaining cognitive deficits or accelerated aging in SMI from that BOLD signal or the functional imaging?

Lisa Eyler 04:31
Yeah, there's been an increased interest in this idea of whether we could just look at these resting signals and how they're coordinated in understanding SMI. Because, for one thing, it's a lot easier than having to have a task that you would have to do. Basically all you have to do is say, "Just keep your eyes open" or "Close your eyes". There's some variability in what people do, but you can just measure the same thing without having to have a task. So it is a popular way of

measuring differences between people with and without SMI and then also looking at aging. There hasn't been as much about accelerated aging and functional connectivity in SMI. I'm not as aware of the data in that. But we actually looked at the difference between people with and without bipolar disorder in terms of their functional connectivity within this default mode network. Specifically between the medial prefrontal cortex and the posterior cingulate, because of mood disorders - sort of the rostral anterior cingulate is an area or caudal anterior cingulate is an area that often comes up in mood disorders. So we thought maybe that connection would be interesting to look at. And interestingly, when we did the functional connectivity analysis the way that it's typically done, which is maybe to collect, say, 8 minutes worth of data. And so you have a time course for region A, say the medial prefrontal cortex, and then you have a time course for region B, the posterior cingulate cortex, and then you just correlate those two time courses across that whole 8 to 10 minutes that you've scanned. That's a typical way of calculating connectivity and you see what the strength of that correlation is. When we did that, we found that there was no group difference between bipolar participants and people without bipolar disorder in the overall strength of the correlation between those two regions. However, we had used a technique that gave us many, many observations within that 8 minute window. So we have about 800 different whole brain images. So 800 different time points within that 8 minutes. So we did what's called dynamic functional connectivity. What that does is it looks at how connectivity changes across the eight minutes. So what you do is you take a little snippet of the time course, say the first one minute of it, or let's say 30 seconds, first 30 seconds, and you look at the correlation of that first 30 seconds. And then you move that window a few seconds, and then you take correlation in the next 30 seconds. And then you move it a little bit and take your correlation there. So you do this sliding window approach so that you get a time course of correlations.

John Bellone 07:22
Like a movie. [laughs]

Lisa Eyler 07:22

Yes, yeah, basically. You can then see the correlation waxing and waning across that whole 8 minutes and how's that happening. Which, if you think about it, it's probably a more accurate way of looking at functional connectivity, because it's very unlikely that you're completely connected for an entire eight minute period, right? It's probably, like, they're sort of talking to each other and then they're not talking to each other because maybe they're going over and talking to this other region. And

they're talking to each other again. So what we found there was that in the bipolar group - and this completely surprised us because I thought that bipolar being a disorder of increased variability, right, more mood variability, going up from highs of mania down to the lows of depression, that they would be more variable across this 8 minute period. But in fact, it was the opposite. They were significantly less variable across it. So they were kind of sticky. There was not as much sort of just touch-and-go. Maybe another way to put it, not as nimble in the connection strength between those things. The connection strength was more steady across the whole 8 minute period. And because I love to look at individual differences, I said, "Well, how about within the bipolar group, the ones that are most like the healthy controls versus those that are - sort of most nimble versus most steady in their connectivity strength?" And what we found, which gets back to your question [laughs] is that the people who had the worst executive function were the ones that were the least nimble in their connectivity. The ones who had the best executive function had more of this healthy pattern of back and forth, sort of touching base and then going away and then coming back.

John Bellone 07:32
And this has been published?

Lisa Eyler 09:11
Yeah.

John Bellone 09:12
What year was that? We'll have to include a link to the article.

Lisa Eyler 09:16
I'll send it to you guys.

John Bellone 09:17
We'll coordinate that later.

Ryan Van Patten 09:18
Yeah. Thanks. That's great. So we've talked about a number of different biomarkers of accelerated aging today. I'd like to touch on just a couple others that we haven't mentioned explicitly, yet - telomere length, oxidative stress, among others. Could you just briefly summarize the literature on these biomarkers and SMI and their impact on the aging process?

Lisa Eyler 09:40

Sure. I mean, there have been a ton of different biomarkers that people have looked at just in regular aging, and people have started to then look at them in SMI. So telomere length is one of those. So every time a cell divides, there's basically a little bit of damage that happens at the ends of the DNA strands and so you get kind of a shortening. People have thought of that as a biological clock. But interestingly it has been shown that early childhood adversity can shorten telomere length as well. So it could be about stress, it could be about kind of aging, or could be about both. Sort of like what we've been talking about with accelerated aging. The literature is pretty mixed for telomere length in SMI. Sometimes people see that there's evidence that's consistent with accelerated aging, and other times not. In fact, there's even some studies that show that the telomeres are longer in people with schizophrenia. So I don't really know what to make of that. Part of it is that some people have suggested that just measuring telomere length is not as accurate as measuring the activity of telomerase. And that telomerase activity may kind of wax and wane over the lifespan. So there's interest in trying to perfect that marker. But people may have heard of telomeres getting shorter when your age, the evidence is not great that that's happening in the same way in people with schizophrenia, bipolar disorder.

Oxidative stress - I mean, there's a whole bunch of other markers of aging that people talk about. Immunosenescence - we've talked a little bit about pro-inflammatory things. The oxidative stress is this idea that these reactive oxygen species and there's ways that you can measure that in the blood. But just like with cytokines, there's some evidence that there's greater oxidative stress in people with schizophrenia or bipolar disorder. But again, we get into the problem of whether this is a peripheral marker of something. That actually we're more interested in what's going on with oxidative stress in the brain. We don't really know exactly how to measure oxidative stress in the brain with say, neuroimaging, at this point. Hopefully, as our interest in this grows, the measures and the techniques that we have will get more specific, and we'll be able to really look at these kinds of things where we want to see them. Or else have good things in the blood that are highly correlated with what we see in the brain.

John Bellone 12:17

Just to start wrapping up, we talked a little bit before about successful aging and what that might look like. Do you have any other insights from this line of research about interventions to prevent or slow accelerated aging? What can we do to slow the aging process, especially in people with SMI? Any other thoughts about that?

Lisa Eyler 12:38

Yeah, I think, again, getting back to this idea of the whole body approach to SMI. So I think these are actually serious physical illnesses as well as serious mental illnesses. We should think about them that way, I think. As I mentioned, this helps in terms of stigma, which where the stigma itself contributes to stress and contributes to a decreased willingness to get help for things. I feel if we can normalize these as just the same as other chronic and physical illnesses, like diabetes or heart disease, we'll have more money for research, we'll have more people being willing to go in and talk to their doctor about the symptoms that they're having. Then hopefully, there'll be more programs that will help to encourage positive lifestyle and resilience with cognitive and emotional resilience, as well as physical things that people can do. You know, when I talk to groups of older adults, with or without serious mental illness, I say, "Look, there's not really any good evidence to say that one thing versus another is more or less effective for helping with your brain health as you get older. But here are some of the things that we have some evidence for. Exercise, good diet, having a little bit of stress, but not too much stress." I do try to emphasize that things like changing up your routine a little bit, doing things that are novel, learning a new language - you know, things that are like slight cognitive stressors may actually be a really good thing for brain health. And trying to encourage that for SMI patients as well.

John Bellone 14:21

It's kind of like inflammation, right? A little bit of stress is adaptive and helps motivate you, but too much is obviously counterproductive.

Ryan Van Patten 14:29

That Yerkes-Dodson curve that applies to many things.

John Bellone 14:32

Exactly.

Ryan Van Patten 14:32

Yeah.

Lisa Eyler 14:33

Yeah. I think people underestimate because they sort of give up on older adults. They certainly give up on people with severe mental illness, and on older adults a little bit, feeling like that they can't really, you know, can't teach an old dog new

tricks. And the literature, I think, really doesn't support that. It's just that we do adult learning a lot differently than we do new learning. So if we used some of the same techniques that we do for teaching kids - like immersion, allowing them to fail multiple times. I think adult learners get these messages that they think that they can't learn. They also are afraid to fail. I'm sure that the same is even more true for people with SMI, when they've had a lot of experiences throughout their lifetime of things not going well. So giving them the opportunity to try new things, I think, is really important. The more we learn from neuroimaging and from inflammation, the more we might be able to promote some of the healing that comes from these lifestyle changes by maybe adjunctive therapies.

So in the realm of inflammation, it may be the case that some people would benefit from anti-inflammatory medications that could then help them to take advantage of the things that lifestyle interventions would do. It may even help them respond better to drugs that are particularly targeted at certain neurotransmitter systems as well. In the realm of neuroimaging, I think what we might find is, again, if we can diagnose, or predict with prognosis, in terms of what people would benefit from what kinds of treatment, we could really use neuroimaging in a good way. And, you never know, there might actually be some usefulness for neural stimulation so that you could directly help to influence certain brain regions that we know are declining with age or because of severe mental illness to help to stimulate that in the context, again, of some behavioral strategies.

Ryan Van Patten 16:38
Yeah. Are you referring to transcranial magnetic or direct current stimulation?

Lisa Eyler 16:42

Yeah, exactly. So using some of those techniques, not a standalone, but as adjunctive to the things that we know already work but they don't work for everybody and they don't work perfectly.

Ryan Van Patten 16:53
Yeah.

John Bellone 16:54

Those are all good ideas. I especially like getting people out of that learned helplessness type of framing. The self-fulfilling prophecy that I'm not going to learn it and that leads them to actually not try as much or not pay attention, and they don't learn it.

Ryan Van Patten 17:06
Isolation, rigidity. Yeah.

John Bellone 17:08
There are so many factors.

Ryan Van Patten 17:11
I'd like to ask a professional development question, Lisa. I'm really interested in interdisciplinary science and work, in general. And in particular, in our field, the intersection between psychology and biology. Your work really reflects that as far as I can see. You're a psychologist by training but you're very well versed in a lot of biology. Can you talk about your experiences and training and how people might mistake you for an MD or neuroscientist at times. So what are your thoughts on this?

Lisa Eyler 17:42
My undergraduate degrees were psychology and zoology, which was sort of human biology, non-plant biology, animal biology. So I always knew that I wanted to put those two together. So I started pretty early as an undergrad with both of those as majors, partly because there actually wasn't an undergraduate neuroscience major when I was at Duke. So I did that and then I did an interdisciplinary concentration in neuroscience, which just meant that I took a couple of classes in neuroscience. And then at that point, I had to decide, “Where am I going to do my graduate work?” I was really interested in the brain and biology of the brain and how that related to behavior. And at the time, there were not a lot of cognitive neuroscience programs, and most of the neuroscience programs were not human focused. So I had to decide between going to medical school versus going to graduate school in psychology. And in the end, I decided to go to graduate school in clinical psychology because I was very interested in working with people and particularly in understanding mental disorders, not just understanding college undergraduates and how their brains work. I didn't think I would be very interested in understanding the liver or the pancreas or the things that I was going to have to learn about to be an MD. I thought maybe I’d do an MD/PhD, but I just thought that was a lot of time learning about other systems that I wasn't interested in. The irony is that now I really kind of wish that I knew about things because...

Ryan Van Patten 19:13
[laughs] Yeah, it's the whole body.

Lisa Eyler 19:15

You know, I'm sitting here saying, "Oh, it's so important to understand the whole body." I would have gotten a lot more knowledge about immunology than I did in my clinical psych program, which was zero of course, because that wasn't really a focus of my program. I think that was the right decision at the time for the types of people that I wanted to learn how to work with. And I'm really glad that I got a strong background in psychopathology as well as behavioral interventions and then of course in neuropsychology with my internship and some of my postdoc work. But I just had to then go back and try and learn a little bit more about genetics and immunology and also neuroanatomy and that sort of thing as I've gone along.

Ryan Van Patten 20:05

Yeah, makes sense.

John Bellone 20:07

So we have a couple of bonus questions for you. Just to finish things here. If you can improve one thing about the field of neuropsychology, what might it be?

Ryan Van Patten 20:15

And to clarify, this is not specific to our topic today. Anything about neuropsychology.

Lisa Eyler 20:20

Well, again, I think this kind of goes back to something I was saying before where I feel like that, to some extent - and maybe this isn't true as much now - but to some extent when I was doing my training in neuropsychology, I felt like there was this big tension between neuroimaging and neuropsychology as if one was going to try to supplant the other. And that neuropsychologists were feeling a little bit like either they had to jump on the neuroimaging bandwagon or get left behind. Or that they sort of had negative feelings towards neuroimaging because they felt like they weren't sufficiently addressing the issues of neuropsychology. So I feel like that one thing that would help with neuropsychology, in general, is if these two groups could come together and they could embrace things. Because, as I say, I see them as completely complementary techniques. And it is true that neuro-imagers could learn a lot from neuropsychologists in terms of tasks development, in terms of interpretation, in terms of understanding the meaning of this, in terms of just understanding what kinds of tasks may be best helped to predict. Doing a lot of neural network kind of modeling to help us better understand the results from neuroimaging. So I feel, like, if we could sort of all come together. And then

similarly, I think the neuroimaging folks can help the clinical neuropsychologist because to the extent that we work to do so. I think the problem is that the neuroimaging folks have gone away to sort of only be interested in research. I think if we could pull those folks back in and say, "There may be some clinical questions that you could contribute to. Let's work together" - to figure out how you could have a complementary thing going on here between the neuropsychologist and the neuroimagers and have more people that are dually-trained or at least can interface with one another really easily.

Ryan Van Patten 22:18
Yeah.

John Bellone 22:19
We had a couple episodes early on about neuroimaging that we kind of tongue in cheek titled "Friends or Foes" in neuroimaging and neuropsychology. To kind of highlight that old way of thinking potentially. That it was antithetical to our positions as neuropsychologists to pursue neuroimaging.

Ryan Van Patten 22:35
But why would we not want to measure the brain in multiple ways, right? You, like, buy a new car, you open up the hood and look at the engine and you also take it for a test drive, not one or the other. It's better.

Lisa Eyler 22:46
Yeah. Good point.

Ryan Van Patten 22:47
So what is one bit of advice that you wish someone told you when you were training, or someone did tell you that really made a difference? Here we're looking for an actionable step that trainees can take that they may not have thought of that could improve their training and performance.

Lisa Eyler 23:03
I think that I have had the good luck to have some awesome mentors. One of the things that I have learned from them, and that I try to pass on to trainees as well, is not to be too short sighted about what the giants on whose shoulders were standing and the history of our field. I think when you have access to something like PubMed, and it comes up in chronological order, you usually start and you read the

first, you know, 10 papers that are there. And there's a lot that has been done before us and a lot of really important ideas that I think sometimes get lost when people are just reading the latest and greatest things. This goes back to this idea of there's this long, rich history of neuropsychology from lesion studies and models of how cognition works that I think most people who are doing the fancy machine learning techniques, when they're applied to neuroimaging data, they're just seeing the neuroimaging data as like data points and not thinking about what it all means. So I guess my advice would be to always think about what is the theory that you're trying to test. You may need to go back some decades to find a good theory because unfortunately people don't develop as many theories anymore. They just are very data driven. Which I think is great because there's a lot of data out there and we want to use those data but I think to also incorporate theory is really important. So taking master classes, reading books... [laughs]

Ryan Van Patten 24:52
What a novel thought. [laughs]

Lisa Eyler 24:54

Gasp. [laughs] Maybe reading books on the history of neuropsychology or sort of the giants of our field and understanding that, so that you can then bring that into the more novel technologies that people are using.

Ryan Van Patten 25:07

Yeah, great answer. So we'll wrap up with one last question. Now that we've covered advice for trainees, I'd like to ask for advice for early career professionals. So the context of this question is that we know the healthcare landscape is changing rapidly. We want neuropsych to remain relevant and useful. Once we're established as neuropsychologists, what steps can we take for ourselves and our field to ensure that we're providing cutting edge scientific and clinical services for the next few decades.

Lisa Eyler 25:37

I'm a really big fan of collaboration. I'm involved in probably way too many projects at this point, but I love the fact that I can use my neuropsychological and neuroimaging skills in so many different fields - I can do studies in healthy aging, I can do intervention studies, I can help to contribute to studies of autism. So what I would suggest for young people starting off is to know what your niche is, but also expand and try to do things with other professionals because that will help you to grow in terms of just exposing you to other populations that you might not do. But it

also gives you some insurance - it's kind of like diversifying your financial portfolio, right? So that if, for whatever reason, your particular topic that you did your fellowship in or that you're starting out with as a young professional, if that topic is no longer hot or sexy and doesn't get the funding, then you can say, "Oh, well, maybe let me work with this person. I'll use some of these same techniques, but apply it to this other field." You know, this kind of happened to me. I was really focused on schizophrenia when I was in my fellowship and right after I became a faculty member. But schizophrenia was a really crowded field, there were a lot of neuropsychologists working on schizophrenia and a lot of neuroimaging people working on schizophrenia. But hardly anybody was doing anything with bipolar disorder. So I started collaborating with some people that were doing work on bipolar disorder here. I started being really interested in how it might be different from or some of the same techniques could be applied that were applied in schizophrenia, but hadn't yet been looked at in bipolar. That helped me to grow into that field. And then from there, I started getting more interested in some of these other things like inflammation and accelerated aging. And now I'm back to also doing things in schizophrenia. So it's not that you can't ever come back. But I think if you diversify your activities, that helps you to be more nimble as you go forward.

Ryan Van Patten 27:48
Yeah. That flexibility is great. Well, this has been an excellent conversation. So educational for us and I know for our listeners. So, thank you so much for your time.

John Bellone 27:57
We covered a lot. A broad range of things. Meandered a little bit, but yeah, that was really, really helpful.

Ryan Van Patten 28:03
Yeah.

Lisa Eyler 28:04
It was my pleasure. It was really nice talking to you guys.

John Bellone 28:06
Great. Thank you.

Ryan Van Patten 28:06
Take care.

Transition Music 28:07

Ryan Van Patten 28:11

So that was a really interesting conversation that we just had. John, I thought that it could be helpful if you and I spent a few minutes talking about how we can take some of these biomarkers that we've been talking about and incorporate them into everyday practice in clinical neuropsychology. A lot of what we talked with Lisa about is very interesting and theoretically relevant. Of course, on NavNeuro we're always thinking about neuropsychology and so I want to maybe elucidate how we can use biomarkers in our daily clinical practice in particular. So a disorder or disease that you and I are both very familiar with, for which I think biomarkers can play a helpful clinical role, is Alzheimer's disease.

John Bellone 29:00

Yeah, and we've talked about this a few other times. We talked about the genetic biomarkers with Meg Collier and then we talked with Adam Brickman about the different diagnostic criteria and the vascular issues and things like that. So potential biomarkers there already.

Ryan Van Patten 29:15

Right, right. So we've hit genetic risk and disclosing genetic risk to patients with Meg Collier and then we hit defining AD based on biomarkers. What I think we can touch on here is how, as a clinician, you or I could benefit from incorporating biomarkers into our report and conceptualization of a patient. So I have some thoughts on this, unless you have anything...

John Bellone 29:42

Yeah, sure. And this could be applicable maybe even to just aging in general. Although AD is one particular example.

Ryan Van Patten 29:49

Right. Like we talked about with Adam Brickman, what we call AD is often mixed dementia. And so, really, you and I are referring to AD / probably some vascular pathology and Lewy body as is typical for a common patient in a neuropsych clinic. But it comes from the AD literature. What I'm thinking of is the common biomarkers that are relevant in the research on Alzheimer's disease related to detecting beta amyloid and tau, of course. So the common biomarkers are PET amyloid, PET tau,

CSF amyloid, CSF tau, and then there is structural MRI related to hippocampal volumes and overall volume loss. I am familiar with some neuropsych clinics that have started to incorporate a few of these biomarkers into their work. In other words, a neuropsychologist who on a regular basis as part of their report gets biomarker data. So the question that I'm posing, and that we can talk about is, are these biomarkers relevant? Can we use them? And if so, how? What are your initial thoughts?

John Bellone 31:02
Yeah, I think the biomarkers that you alluded to - you know, having a sense of amyloid and tau burden - those are thought to be the hallmarks of Alzheimer's disease. I think more information is usually better and more data that we can tie to our clinical work. I think it could definitely help our incremental validity in terms of what we add to the picture if we have a good sense of the full picture.

Ryan Van Patten 31:25
Right, right. So if listeners have heard our conversation with Adam Brickman, which I'd recommend, we think about Alzheimer's disease in two different ways. We think about the clinical syndrome - the memory loss, ultimately dysexecutive functioning, and then global cognitive decline later on in the disease. But before that, we have the pathological Alzheimer's disease. And that's what we're measuring with biomarkers.

John Bellone 31:48
What's going on under the hood.

Ryan Van Patten 31:50
Exactly. Yeah. So in neuropsych, we're measuring the clinical syndrome. So if we can also have data pertaining to the other piece of the puzzle - what's going on under the hood - I think that makes our understanding of what's happening with a single person a lot stronger. There's one particular example I've thought of, like a type of case where this can be helpful. The least invasive way, as of right now, to get amyloid and tau is through a spinal tap. My understanding is that we're working on blood-based biomarkers for amyloid and tau, but unless something has changed and there are recent papers that I haven't seen yet, that's not quite at the level of precision and accuracy to be used.

John Bellone 32:35
And spinal tap just assesses the cerebrospinal fluid, CSF.

Ryan Van Patten 32:39
Right. So these clinics I referred to, some neuropsychologists there regularly get data pertaining to CSF - amyloid and tau - for their patients. And you might wonder if you have that data, like, how can it be useful? Well, what those data are telling you is what's going on under the hood - is there amyloid accumulation and tau accumulation in the brain of this person? It's not uncommon in a lot of memory loss clinics for us to see people who may seem to be "worried well". Or, in other words, they have some subjective cognitive decline but they're doing pretty well in testing, who then have some degree of amyloid and tau burden that you'd see with these biomarkers. What I think is a useful way to use this information is that person, who I'm referring to, that type of person has some AD pathology, but doesn't yet have the AD clinical syndrome. And we know that pathology precedes the syndrome. So they are at much greater risk of having cognitive decline in the relatively near future if they have high premorbid functioning like a lot of patients do in particular clinics - high education, cognitive stimulation, occupational attainment in their history. They have a lot of cognitive reserve. The literature shows us that those people, although they decline later, when they do decline, they really fall off a cliff - they decline really quickly. So this patient, this person who I made up, who's sort of a representation of a lot of cases we might see, their cognitive data look normal, but they have elevated CSF - amyloid, and tau - they are at risk for coming to the precipice of that cliff cognitively and kind of falling off. So I've thought for a while, when I see cases like that, I will be sure to have a follow up with that person much sooner than I otherwise would. I'm not suggesting we tell that person they have AD and worry them and create a big show of it. We can communicate this to them in whatever way makes the most sense. But I think short follow up periods with repeat assessments for people like that are likely very beneficial to them. To me, as we were talking to Lisa, that came to my mind is a way we can be actively using biomarkers and clinical neuropsych on a daily basis right now.

John Bellone 32:39
Right. Because you had asked her about the potential future benefit of a functional MRI in our clinical work. But this could be another potential application of imaging, for clinical decision making. Yeah.

Ryan Van Patten 35:21
Right. Of course, PET amyloid, PET tau could serve the same purpose. They're just more invasive. John, I know you've mentioned to me offline about how genetic status like APOE status can be helpful clinically. What's been your experience with that?

John Bellone 35:36
Right. Knowing the amyloid burden in a similar fashion to knowing the genetic profile in terms of - we had mentioned we had talked to Meg Collier about the elevated risk, I'd encourage listeners to go back and listen to that episode, because we get a lot of background about just genetic testing in general. So most people in the population don't have elevated risk for Alzheimer's disease. If you have one copy of APOE-4, you are at about three times the risk compared to the normal population. If you have two copies of E4, then you're at about 12 times, 12 fold the risk of developing Alzheimer's disease as the general population. So as a clinician, I think it's helpful to have that information. There was a case recently where a woman came in who was complaining of subjective cognitive impairment. She said that she had genetic testing and it was positive for amyloid. It was helpful for me to know that it was only one copy. So I knew that she wasn't at the most elevated risk. She was at a moderate elevated risk.

Ryan Van Patten 36:43
You said it was positive for amyloid? You mean it was positive for the...

John Bellone 36:46
Sorry, for the APOE-4. Right. She had one copy of the E4 allele. Thanks for clarifying that. She was doing fine on testing, but it helped in my feedback session because I could tell her that, "Yes, you are at somewhat of an elevated risk compared to others, but that by no means guarantees that you're going to develop Alzheimer's disease. I'm not seeing any evidence of it right now. You don't need to worry about this." Because she was really concerned. She thought that she had Alzheimer's disease right now.

Ryan Van Patten 37:10
Did she think APOE was deterministic?

John Bellone 37:12
Yes.

Ryan Van Patten 37:12
Okay.

John Bellone 37:12
Exactly. So, right, if you remember from that previous episode, it's not deterministic. Meaning that if you have this genetic predisposition, it's not determined that you're going to get that disease, but it does increase risk to some point. Anyway, that was helpful for me more in the feedback session to kind of talk her through that. It was helpful to have that extra piece of data. If I had also had the level of amyloid burden - you know, maybe she was normal. Maybe she wasn't positive for amyloid burden if she had taken an amyloid PET scan, for example. That would have been extra data that I could have given her as evidence that there's no evidence right now. Basically, it was the absence of evidence of Alzheimer's disease currently. So, I don't know. I just see this as extra information to help me.

Ryan Van Patten 38:02
Right. Yeah. So we wanted to talk this through to give a few examples of how we think that good evidence-based biomarkers can be useful for us as clinical neuropsychologists right now. And to tie this back into the conversation with Lisa, she has some ideas about how biomarkers could be useful diagnostically for neurodevelopmental and psychiatric conditions in the future. Right now, the literature is not developed enough such that we can take a particular biomarker of a 4-year old or 2-year old and predict who will get ASD or who won't.

John Bellone 38:40
Autism spectrum disorder.

Ryan Van Patten 38:41
Right. But if and when we're at that point in time - it's sort of similar to early detection of AD. The AD literature feels more developed in that way. Obviously, a neurodegenerative condition is very different from a neurodevelopmental condition. But the general idea of preclinical detection of illness, followed by intervention to mediate or prevent, slow, attenuate that later condition - that general idea plays out in several disorders.

John Bellone 39:14
Right. If you could tell, based on the inflammatory profile, that a child at 1-years old is going to develop autism by age 2 - they're going to start developing the

symptoms or something - that would be extra information for you to begin resources now, start early intervention.

Ryan Van Patten 39:32

Imagine the power of that. Schizophrenia is another great example. So there are some early signs that we've seen. I'm familiar with some research in people who later develop schizophrenia, which we know usually manifests in early adulthood - take those people and look back at some of their behaviors and how they acted as children and there's some research on odd behaviors and unusual profiles. Imagine that literature is more developed so that there's a screening instrument or battery that everyone goes through at age 8 and it determines your risk for later psychosis. And those people who are at high risk, the ability to intervene in that population, as opposed to waiting until someone has had a psychotic episode and they're homeless and they've been living this way for decades, right? It's just so much easier to intervene early.

John Bellone 40:30

Yeah. Right. So I think we're on the same page. The more information, the better. Especially the biomarker information. The research is going to continue to develop. So over the next years and decades, I think we're going to get a lot of biomarkers to help us in the decision making process. I guess one potential limitation is the costs of that. So you mentioned that there's a facility that you know that has a lot of information, but usually it requires a nice grant from a research project, right?

Ryan Van Patten 41:02

To acquire biomarkers, typically, especially PET imaging. Yeah. So there's also other lines of research on AD to make biomarker acquisition more affordable. So CSF is certainly less invasive and more affordable than PET. And the line of research I'm thinking of are people working on blood-based biomarkers of amyloid in AD, so that it's more accessible to more people.

John Bellone 41:27

Right. I mean, one downside is the potential cost. But, as you said, I think that'll get cheaper and cheaper and be more accessible. You know, as that happens, maybe it'll be in the hands of more people. Like the genetics stuff, we have direct-to-consumer genetic testing. I wonder if that's going to be the same for the blood-based biomarkers. And people are going to need that education, right?

Ryan Van Patten 41:50
Right. Imagine you prick your finger at home and send a drop of blood into some lab, and then they tell you how much amyloid and tau you have in your brain.

John Bellone 41:58
Exactly.

Ryan Van Patten 41:58
But, you're right, then there could be widespread hysteria, like there already is to some extent around 23andme and the DTC genetic.

John Bellone 42:06
Yeah, the direct-to-consumer genetic testing. Right. So I see a lot of parallels here. It'll have to be done in a clinically mindful way. But I don't see why it couldn't.

Ryan Van Patten 42:18
Right. And certainly, before we get to the stage of there being direct-to-consumer blood based biomarkers of AD, right now, it's helpful for our trained clinicians to use that information. So what we've tried to do here is use AD as a more developed case of biomarkers where the literature is further along. And then to leverage that to talk a little bit about biomarkers in psychiatric illness. Because, hopefully, in the future, we can have biomarkers in psychiatry that go hand in hand with what clinical psychologists do - the phenotyping, the observable piece. It's just like with neuroimaging versus neuropsychology, we're not opposed. We should embrace and work with biological data.

John Bellone 43:02
Right. Ultimately the question is, what is the purpose of those biomarkers? Right? It doesn't really mean anything to have amyloid your brain if it doesn't cause the cognitive changes that people care about.

Ryan Van Patten 43:17
Thanks, Adam. [laughs]

John Bellone 43:17
Yeah, exactly. Hearing his echo. So, hopefully, as interventions come about, as new treatments are developed, I think it'll be extra important for us to have access to that kind of data for Alzheimer's disease in particular, but we talked about autism

and some of the psychiatric issues. I think the earlier, as you mentioned earlier, you can detect it or at least detect it with some amount of sensitivity and specificity, the earlier you can get the resources and the early intervention started. So I can see the application maybe even more for the neurodevelopmental and psychiatric issues.

Ryan Van Patten 43:57

Imaging learning disabilities. It can identify those early. That might be the best neurodevelopmental case, maybe intellectual disability, but with learning disabilities it's really all about getting resources to that person and the specific tutoring before a child falls behind two, three, four grade levels in reading. If we had intensive resources that were built into school systems because we have identified them at age 3, we could prevent learning disabilities in reading, writing, or math from ever even really developing.

John Bellone 44:30

Yeah, great point. So, yeah, I think neuropsychologists should not be opposed to biological biomarkers. We should be more and more open to using it clinically in addition to research-wise.

Ryan Van Patten 44:45

This is a really, really exciting area, as far as I'm concerned. Taking the psychological and phenotypic data that we are so good at collecting as clinical psychologists and then integrating it with, as technology develops, more and more data-based biological markers of functioning. So I look forward to the future. We'll definitely continue to bring biomarkers in our conversations and NavNeuro pretty frequently. It's relevant.

John Bellone 45:14

Yeah. Especially as new biomarkers are developed. It's going to be great. I think over the next 10 years, I think we're going to see a huge increase in the biomarkers for a number of different psychiatric and neurocognitive issues.

Ryan Van Patten 45:27

Yeah, there's a lot to look forward to for sure.

So, that does it for our conversation with Lisa and our little wrap up here. We thank you so much for listening as always, and join us next time as we continue to navigate the brain and behavior.

Exit Music 45:43

John Bellone 46:07

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Ryan Van Patten 46:18

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